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TITLE: Prostate Cancer and Pesticide Exposure in Diverse Populations in California's Central Valley

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**14. ABSTRACT**
This project is a pilot case-control study of pesticide exposure and prostate cancer, hypothesizing that (1) poor measurement of pesticide exposure in studies of prostate cancer risk factors explains null findings to date; (2) a proposed method of recruiting and approaching cases and controls to a large population-based case-control study will result in acceptable response rates, but also will be biased; (3) We will be able to obtain sufficient DNA from mailed buccal swab kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future. We found that there are substantial increased risks of prostate cancer with long term exposure to a number of pesticides, despite the limitations of our pilot study (namely, small sample size). We addressed selection bias, and after doing so, still noted increased risks for prostate cancer with certain pesticides. Our study design appears to ensure that a large scale study would both be successful, and is warranted.

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## In this final report, we outline progress since the inception of the award,

In short, we have completed a total of 170 case and 204 control interviews, and have updated analyses (mid year, for the PCRP meeting in Atlanta) based on the final eligible set of 170 cases and 162 controls. We used only 162 of the 204 controls because the remaining 42 were outside the age range of the cases. Initially we had included them in analyses, but their inclusion was clearly unwarranted. In future work we will be able to use these controls (we are planning an R01-style grant to continue the study, and that will have a wider age range of cases). We incorporate data from all 170 cases and 162 controls into analyses of pesticide exposure and prostate cancer, and completed our other analyses of the representativeness of the cases and controls.

### A. INTRODUCTION:

There is some evidence that pesticide exposure is a risk factor for prostate cancer. Some pesticides, classified as endocrine-disrupting chemicals (EDCs), can affect normal hormone function. Variations in hormone levels affect prostate cancer risk, since normal growth of the prostate gland is dependent on a critical balance of androgen levels. Pesticides may affect hormone function by mimicking hormones, affecting enzyme systems involved in hormone metabolism, or directly affecting the brain regions involved in hormone functioning. A possible involvement of pesticides in prostate carcinogenesis is suggested by findings among farmers in studies of occupation and prostate cancer. The overall association reported by recent meta-analyses of farming and prostate cancer report a summary relative risk of 1.1, but the majority of studies with relatively large numbers of subjects consistently showed excess relative risks of prostate cancer ranging from 1.06 to 5.0. This limited evidence may well be inconclusive because of the difficulty in measuring true pesticide exposure – all these studies relied on self-reported occupational exposure, resulting in bias towards the null, and the omission of non-occupational environmental exposures (e.g. residences downwind of application sites). A large-scale population-based case-control study in California's Central Valley, the nation's leading user of pesticides, simultaneously assessing genetic and environmental risk factors for prostate cancer in an ethnically-diverse population with varying occupational and residential exposures to pesticides would go a long way to further refining knowledge of prostate cancer etiology. However, the complexities of such a study warrant excellent pilot data. We have been evaluating for some time now the use of Pesticide Use Reporting (PUR) data, refined by additional data on land use, in a Geographical Information System (GIS) to obtain objective historical pesticide exposure estimates.

This project is a pilot case-control study of pesticide exposure and prostate cancer, hypothesizing that (1) attenuation of estimates of the relative risk of pesticide exposure and prostate cancer in the absence of full (residential and occupational) historical pesticide exposures is significant, and could explain null

findings to date; (2) our proposed method of recruiting and approaching cases and controls to a large population-based case-control study will result in acceptable response rates, but our sample will be biased with respect to socioeconomic status, race, and disease characteristics – we will preferentially recruit higher SES, white males with localized disease; (3) We will be able to obtain sufficient DNA from mailed buccal swab kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future.

**B. PROGRESS TOWARDS SPECIFIC AIMS.**

Specific Aims outlined in the Statement of Work were:
1. show that **historical** residential and PUR/land use data provides substantial **reduction in exposure misclassification** in both prostate cancer cases and controls compared to estimates based only on **current** residential addresses and PUR/land use data information alone
2. demonstrate the **feasibility** of conducting a case-control study of biochemical and environmental risk factors (especially pesticide exposure), susceptibility genes, and their interactions for prostate cancer in the Central Valley. In particular, we will demonstrate the feasibility of our **case selection method**, **control selection method**, and **methods of obtaining buccal DNA** for genetic hypotheses.

## Accomplishments:

### *1. Development of the GIS for determining exposure to pesticides.*

The process for estimating pesticide exposure in this study relies on combining data from California's Pesticide Use Registry (PUR) and land use (PLSS) data to determine the exact location of applied pesticides.

We developed an automated program for combining the PUR and PLSS data within a GIS – this automated process was custom programmed in ArcGIS, and can be updated with new PUR and PLSS data as they become available. It also allows us to use any historical residential data (e.g. from other case-control studies) and generate pesticide exposure estimates.

We are currently using this GIS in this project to determine pesticide exposures, and in other studies where pesticide exposures are required (e.g. an ongoing study of risk factors for breast cancer in the inhabitants of California's Central Valley).

We further refined our computer model so that it can run on many thousands of observations (previously this was not possible because of limitations in ArcGIS – we removed those limitations by programming a separate interface in .Net). This was required so that we can generate pesticide analyses for thousands of population-based points (randomly selected tax assessor parcel locations) for comparison of exposure assessment misclassification in the cases and controls (Aim 2). This also means that the code can be more easily shared with other investigators who wish to use the approach.

### *2. Development of questionnaire*

We developed, piloted and refined a questionnaire that ascertained prostate cancer risk factor information, as well as detailed historical residential data (to incorporate into the pesticide exposure assessment) and detailed information on in-home and occupational exposure to pesticides. This questionnaire has been used throughout the study, and will be available as a deliverable at the conclusion of the study. Now the questionnaire has been used among 374 individuals (170 cases and 204 controls), and we have noted changes required for clarity. The questionnaire has been shared with other investigators (Dr Ritz at UCLA for example, who is using our residential history questionnaire to determine exposures for a study of Parkinson's Disease and pesticide exposures).

In addition, we have developed a data entry system in SAS for the questionnaire that can also be made available upon request (there are many hundreds of items in the questionnaire, and an accompanying database design will greatly reduce the effort of anyone wishing to use it).

Both the questionnaire, and accompanying SAS program, are available on request from the PI.

### *3. Recruitment and interview of prostate cancer cases*

Aim 2. was to demonstrate the feasibility of conducting a case-control study of biochemical and environmental risk factors (especially pesticide exposure), susceptibility genes, and their interactions for prostate cancer in the Central Valley. In particular, we wished to demonstrate the feasibility of our case selection method, and methods of obtaining buccal DNA for genetic hypotheses.

We estimated we would be able to obtain 60 cases and controls, and in fact have recruited and interviewed 170 cases, and 204 controls.

We analyzed the representativeness of the cases included in our study (the response rate, after removing those cases we had no contact information for, was 64% - which is high for this kind of study which did not use rapid case ascertainment – but tells us nothing of the probability that we included a biased sample of cases). The results are summarized in Table 1, which compares the cases we obtained from the population-based Central California Cancer Registry with the cases we were able to interview ('surveyed cases') and those finally included in the analysis above (those providing informed consent and saliva sample for DNA analyses).

Table 1 Comparison of interviewed prostate cases with those selected from the population-based Cancer Registry.

| | | Attempted cases | | Analysis cases | |
|---|---|---|---|---|---|
| Prostate Cancer, N (%) | | NH white | Hispanic | NH white | Hispanic |
| Diagnosis Age, y | 60-64 | 92 (27.46) | 58 (25.78) | 35 (28.23) | 15 (32.61) |
| | 65-69 | 130 (38.81) | 84 (37.33) | 47 (37.90) | 18 (39.13) |
| | 70-74 | 113 (33.73) | 63 (36.89) | 42 (33.87) | 13 (28.26) |
| Stage | IN SITU | | | 0 (0.00) | 0 (0.00) |

| | | | | | |
|---|---|---|---|---|---|
| | LOCALIZED | 277 (82.69) | 180 (80.00) | 104 (83.87) | 38 (82.61) |
| | REGIONAL, DIRECT EXTENSIONS ONLY | 38 (11.34) | 29 (12.89) | 14 (11.29) | 4 (8.70) |
| | REGIONAL, NODES ONLY | 4 (1.19) | 0 (0.00) | 2 (1.61) | 0 (0.00) |
| | REGIONAL, DIRECT EXTENSION AND NODES | 2 (0.60) | 4 (1.78) | 2 (1.61) | 1 (2.17) |
| | DISTANT METASTASES OR SYSTEMIC DISEASE (REMOTE) | 8 (2.39) | 8 (3.56) | 1 (0.81) | 2 (4.35) |
| | UNSTAGEABLE; UNKNOWN | 5 (1.49) | 4 (1.78) | 1 (0.81) | 1 (2.17) |
| | MISSING | 1 (0.30) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Birthplace | UNITED STATES | 159 (47.46) | 70 (31.11) | 62 (50.00) | 16 (34.78) |
| | OTHER | 11 (3.28) | 58 (25.78) | 5 (4.03) | 19 (41.30) |
| | MISSING | 165 (49.25) | 97 (43.11) | 57 (45.97) | 11 (23.91) |
| | | 335 | 225 | 124 | 46 |

While we expected that we would preferentially select cases with a lower stage disease and cases more likely to be younger, and with a birthplace in the U.S. (the former two affecting generalizablilty of general prostate cancer risk factor information, the latter affecting our lifetime estimates of pesticide exposure from residential history), we found instead that there were few, if any, differences between the population-based sample of cases, and those included in the final analysis.

This leads us to conclude that our case-control method yields a relatively unbiased source of cases and controls for this study design. While the response rate in the Hispanic population was lower than among the non-Hispanic White population, this is a misleading figure because we only added Hispanic cases near the end of the study, and had less time to recruit them. The recruitment-time specific response rates were very similar in Hispanic and non-Hispanic white populations in this study.

**Extracting DNA from saliva specimens**

We used the Oragene saliva kit to obtain specimens from all participants. We mailed participants the kits, and they were returned to us by mail. Specimens were stored at room temperature for 1-3 weeks before being processed by the lab.

We quantified DNA yield from saliva specimens. The overall mean yield was 29,817 ng, with a minimum of 335 ng, a maximum of 227,441 ng. 58% of samples had greater than 20,000 ng.

## *4. The analyses of pesticide exposure and prostate cancer risk*

We used our GIS-based Residential Ambient Pesticide Exposure Software (GRAPES) tool to estimate lifetime and age-specific exposures to a variety of pesticides and herbicides using residential history information, and combined data from the California Pesticide Use Registry (PUR) and Land Use Information, both available for years from 1974 to 1999. We have previously described how the latter are combined to produce an accurate estimate of year-specific pesticide application in small geographical areas (Ritz and Rull). Our GRAPES model combines PUR and LU data for each reported residence for the lifetime history of cases and controls.

We hypothesized that previous studies of prostate cancer and pesticide exposure that only considered exposures occurring at time of diagnosis would underestimate the true relationship due to (1) random misclassification (inaccurate estimation of exposure) resulting in bias towards the null (2) specifically underestimating exposure in cases only, resulting in a differential bias, but still with a net effect of bias towards the null.

In our analyses of these effects, we focused on the main pesticide groupings that have been shown to have relationships with prostate cancer, namely methyl bromide, captan, and simazine; Other pesticidesand groupings of pesticides includeorganochlorines, r.

We calculated exposures for (1) diagnosis year only (2) life time (ie age 0 to age at diagnosis) – for this exposure, we assumed that year 1974 pesticide use continued back through time to the earliest year required (3) the period 1974 to 1999 only (the years for which PUR/LU data were available (4) accumulated exposures in the period 10 years prior to diagnosis only (5) accumulated exposures in the period 15 years prior to diagnosis only. Some of the individuals have missing years of exposure due to unknown address or living out of the study areas. Our strategy for dealing with missing data is the Average Valid Year (AVY) approach: calculate the average from all the observable years of exposure.

The PUR/LU data were available for 1974-1999 only. Our approach to estimate the period outside 1974 - 1999 is similar to a technique called “last observation carried forward” (LOCF), or equivalently, first observation carried backward (FOCB). For the years earlier than 1974, we use the 1974 PUR and LU data, for the years later than 1999, we use the 1999 PUR and LU data. The slight difference is that we only carry over the PUR and LU data and apply them to the address history that changes over time.

The pesticide exposures for cases and controls included in the analysis is summarized in Table 2. We included the mean exposure level, the standard deviation, the maximum exposure over the years.

***Table 2: Estimated exposure levels for key pesticides in cases and controls in California's Central Valley, recruited 2005 - 2006 (in pounds)***

| | | Mean | Std Dev | Max (*) | Count (†) |
|---|---|---|---|---|---|
| ***Methyl Bromide*** | | | | | |
| ***Case*** | *DX Year* | 76.60 | 461.26 | 5558.17 | 163 |
| | *1974 - 1999* | 32.69 | 94.23 | 586.37 | 150 |
| | *Life time* | 22.47 | 69.69 | 507.10 | 166 |
| | *10 years prior to DX* | 12.69 | 50.03 | 491.79 | 149 |
| | *15 years prior to DX* | 7.97 | 51.80 | 586.37 | 138 |
| ***Control*** | *DX Year* | 43.76 | 338.29 | 3913.93 | 146 |
| | *1974 - 1999* | 23.59 | 84.32 | 692.40 | 155 |
| | *Life time* | 14.81 | 49.34 | 393.04 | 161 |
| | *10 years prior to DX* | 9.22 | 38.09 | 336.51 | 153 |
| | *15 years prior to DX* | 6.09 | 31.94 | 346.22 | 143 |
| ***Captan*** | | | | | |
| ***Case*** | *DX Year* | 3.76 | 20.17 | 208.44 | 163 |
| | *1974 - 1999* | 2.22 | 5.89 | 39.32 | 150 |
| | *Life time* | 1.42 | 4.33 | 31.80 | 166 |
| | *10 years prior to DX* | 1.48 | 5.11 | 37.47 | 149 |
| | *15 years prior to DX* | 1.53 | 5.82 | 50.34 | 138 |
| ***Control*** | *DX Year* | 1.70 | 13.31 | 147.59 | 146 |
| | *1974 - 1999* | 1.21 | 4.34 | 37.88 | 155 |
| | *Life time* | 0.99 | 4.62 | 44.02 | 161 |
| | *10 years prior to DX* | 0.59 | 1.92 | 16.50 | 153 |
| | *15 years prior to DX* | 0.46 | 1.47 | 13.70 | 143 |
| ***Simazine*** | | | | | |
| ***Case*** | *DX Year* | 5.84 | 17.31 | 104.31 | 163 |
| | *1974 - 1999* | 2.44 | 6.66 | 44.60 | 150 |
| | *Life time* | 2.14 | 4.77 | 27.85 | 166 |
| | *10 years prior to DX* | 1.56 | 3.82 | 28.84 | 149 |
| | *15 years prior to DX* | 1.39 | 4.04 | 31.85 | 138 |
| ***Control*** | *DX Year* | 3.26 | 12.22 | 87.39 | 146 |
| | *1974 - 1999* | 2.15 | 8.31 | 83.50 | 155 |
| | *Life time* | 2.23 | 6.09 | 37.74 | 161 |
| | *10 years prior to DX* | 1.61 | 5.12 | 45.77 | 153 |
| | *15 years prior to DX* | 1.40 | 5.24 | 51.21 | 143 |
| ***Organochlorine*** | | | | | |
| ***Case*** | *DX Year* | 2.36 | 16.57 | 203.41 | 163 |
| | *1974 - 1999* | 4.19 | 8.60 | 48.27 | 150 |
| | *Life time* | 6.35 | 18.77 | 203.41 | 166 |
| | *10 years prior to DX* | 6.76 | 13.66 | 106.35 | 149 |
| | *15 years prior to DX* | 7.51 | 15.79 | 118.16 | 138 |
| ***Control*** | *DX Year* | 0.90 | 5.74 | 64.85 | 146 |
| | *1974 - 1999* | 1.27 | 3.40 | 19.79 | 155 |
| | *Life time* | 4.16 | 10.55 | 77.96 | 161 |
| | *10 years prior to DX* | 4.84 | 11.73 | 94.21 | 153 |
| | *15 years prior to DX* | 5.49 | 13.55 | 104.83 | 143 |
| ***Paraquat Dichloride*** | | | | | |
| ***Case*** | *DX Year* | 3.82 | 16.91 | 151.44 | 163 |
| | *1974 - 1999* | 1.87 | 4.46 | 22.12 | 150 |

| | | | | | |
|---|---|---|---|---|---|
| | *Life time* | 2.14 | 11.01 | 136.67 | 166 |
| | *10 years prior to DX* | 1.08 | 2.52 | 22.07 | 149 |
| | *15 years prior to DX* | 0.87 | 1.59 | 9.55 | 138 |
| | *DX Year* | 1.29 | 4.51 | 32.67 | 146 |
| | *1974 - 1999* | 1.37 | 5.64 | 64.75 | 155 |
| ***Control*** | *Life time* | 1.08 | 3.48 | 36.88 | 161 |
| | *10 years prior to DX* | 0.78 | 2.38 | 23.21 | 153 |
| | *15 years prior to DX* | 0.62 | 1.58 | 10.78 | 143 |
| ***Benzimidazole Benomyl*** | | | | | |
| | *DX Year* | 0.28 | 1.57 | 15.82 | 163 |
| | *1974 - 1999* | 0.60 | 1.77 | 11.03 | 150 |
| ***Case*** | *Life time* | 0.41 | 1.04 | 6.79 | 166 |
| | *10 years prior to DX* | 0.51 | 1.19 | 6.59 | 149 |
| | *15 years prior to DX* | 0.50 | 1.30 | 10.62 | 138 |
| | *DX Year* | 0.22 | 1.38 | 11.78 | 146 |
| | *1974 - 1999* | 0.59 | 2.64 | 27.20 | 155 |
| ***Control*** | *Life time* | 0.36 | 1.22 | 9.82 | 161 |
| | *10 years prior to DX* | 0.37 | 1.27 | 11.41 | 153 |
| | *15 years prior to DX* | 0.34 | 1.27 | 12.40 | 143 |
| ***Maneb*** | | | | | |
| | *DX Year* | 0.18 | 1.18 | 10.30 | 163 |
| | *1974 - 1999* | 0.37 | 1.88 | 15.88 | 150 |
| ***Case*** | *Life time* | 0.30 | 1.58 | 12.72 | 166 |
| | *10 years prior to DX* | 0.39 | 2.21 | 17.47 | 149 |
| | *15 years prior to DX* | 0.52 | 2.87 | 22.26 | 138 |
| | *DX Year* | 0.01 | 0.08 | 1.01 | 146 |
| | *1974 - 1999* | 0.88 | 7.19 | 87.68 | 155 |
| ***Control*** | *Life time* | 0.49 | 3.79 | 47.39 | 161 |
| | *10 years prior to DX* | 0.40 | 2.68 | 31.92 | 153 |
| | *15 years prior to DX* | 0.19 | 0.76 | 6.43 | 143 |

* The minimum exposure is always 0, namely unexposed

† Number of the patients with observable exposure

We then calculated crude odds ratios (ORs) and ORs adjusted for age, race (white or non-white), and home pesticide use (three categories: no exposure, maybe, likely). These results are outlined in Tables 3a-g for each of the exposure time periods noted above, which also provide 95% CIs for effect estimates, and p-values for the difference between exposure levels. Because the distribution of exposure was skewed, we provide both an estimate of the relative risk for any exposure (jpositive vs. 0 exposure), and for two levels of exposure (medium and high, depending on the distribution of exposure), both compared to 0 exposure as a baseline.

***Table 3a. Relative risk estimates for prostate cancer with exposure to Methyl Bromide in California's Central Valley 2005 - 2006***

***Methyl Bromide***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 131 | 137 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 32 | 9 | **3.72** | 1.71 | 8.09 | 0.00 | **3.41** | 1.55 | 7.48 | 0.00 |
| *Low (†)* | 7 | 3 | **2.44** | 0.62 | 9.64 | 0.00 | **2.53** | 0.63 | 10.16 | 0.01 |
| *High (†)* | 25 | 6 | **4.36** | 1.73 | 10.96 | | **3.83** | 1.51 | 9.73 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 63 | 85 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 87 | 70 | **1.68** | 1.07 | 2.64 | 0.03 | **1.63** | 1.03 | 2.58 | 0.04 |
| *Low* | 45 | 35 | **1.73** | 1.00 | 3.00 | 0.08 | **1.75** | 1.00 | 3.06 | 0.11 |
| *High* | 42 | 35 | **1.62** | 0.93 | 2.82 | | **1.51** | 0.86 | 2.65 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 76 | 88 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 90 | 73 | **1.43** | 0.92 | 2.21 | 0.11 | **1.39** | 0.89 | 2.16 | 0.15 |
| *Low* | 49 | 42 | **1.35** | 0.81 | 2.26 | 0.26 | **1.38** | 0.82 | 2.33 | 0.35 |
| *High* | 41 | 31 | **1.53** | 0.88 | 2.68 | | **1.40** | 0.79 | 2.47 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 76 | 86 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 73 | 67 | **1.23** | 0.78 | 1.94 | 0.37 | **1.16** | 0.73 | 1.85 | 0.52 |
| *Low* | 49 | 50 | **1.11** | 0.67 | 1.83 | 0.42 | **1.08** | 0.65 | 1.80 | 0.64 |
| *High* | 24 | 17 | **1.60** | 0.80 | 3.20 | | **1.41** | 0.69 | 2.86 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 77 | 84 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 61 | 59 | **1.13** | 0.70 | 1.81 | 0.62 | **1.04** | 0.64 | 1.69 | 0.88 |
| *Low* | 48 | 49 | **1.07** | 0.65 | 1.77 | 0.74 | **1.01** | 0.60 | 1.68 | 0.92 |
| *High* | 13 | 10 | **1.42** | 0.59 | 3.42 | | **1.21** | 0.48 | 3.00 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 8 pounds; High exposure: ≥ 8 pounds

***Table 3b. Relative risk estimates for prostate cancer with exposure to Captan in California's Central Valley 2005 – 2006***

***Captan***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 144 | 136 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 19 | 10 | **1.79** | 0.81 | 4.00 | 0.15 | **1.84** | 0.82 | 4.15 | 0.14 |
| *Low (†)* | 2 | 2 | **0.94** | 0.13 | 6.80 | 0.29 | **1.24** | 0.17 | 9.10 | 0.31 |
| *High (†)* | 17 | 8 | **2.01** | 0.84 | 4.80 | | **1.98** | 0.82 | 4.78 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 92 | 104 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 58 | 51 | **1.29** | 0.80 | 2.05 | 0.29 | **1.20** | 0.74 | 1.94 | 0.45 |
| *Low* | 19 | 29 | **0.74** | 0.39 | 1.41 | 0.03 | **0.68** | 0.35 | 1.30 | 0.03 |
| *High* | 39 | 22 | **2.00** | 1.11 | 3.63 | | **1.91** | 1.05 | 3.50 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 106 | 106 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 60 | 55 | **1.09** | 0.69 | 1.72 | 0.71 | **1.03** | 0.65 | 1.64 | 0.91 |
| *Low* | 27 | 34 | **0.79** | 0.45 | 1.41 | 0.19 | **0.75** | 0.42 | 1.35 | 0.21 |
| *High* | 33 | 21 | **1.57** | 0.85 | 2.89 | | **1.48** | 0.80 | 2.77 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 93 | 101 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 56 | 52 | **1.17** | 0.73 | 1.87 | 0.51 | **1.10** | 0.68 | 1.78 | 0.70 |
| *Low* | 25 | 31 | **0.88** | 0.48 | 1.59 | 0.25 | **0.82** | 0.44 | 1.50 | 0.26 |
| *High* | 31 | 21 | **1.60** | 0.86 | 2.98 | | **1.53** | 0.81 | 2.87 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 85 | 95 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 53 | 48 | **1.23** | 0.76 | 2.01 | 0.40 | **1.13** | 0.68 | 1.86 | 0.64 |
| *Low* | 21 | 30 | **0.78** | 0.42 | 1.47 | 0.05 | **0.71** | 0.37 | 1.36 | 0.07 |
| *High* | 32 | 18 | **1.99** | 1.04 | 3.80 | | **1.82** | 0.94 | 3.52 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 1 pounds; High exposure: ≥ 1 pounds

***Table 3c. Relative risk estimates for prostate cancer with exposure to Simazine in California's Central Valley 2005 - 2006***

***Simazine***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 120 | 124 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 43 | 22 | **2.02** | 1.14 | 3.58 | 0.02 | **1.90** | 1.06 | 3.39 | 0.03 |
| *Low (†)* | 5 | 5 | **1.03** | 0.29 | 3.66 | 0.03 | **0.87** | 0.24 | 3.19 | 0.05 |
| *High (†)* | 38 | 17 | **2.31** | 1.24 | 4.31 | | **2.21** | 1.17 | 4.17 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 82 | 87 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 68 | 68 | **1.06** | 0.68 | 1.67 | 0.80 | **1.00** | 0.63 | 1.58 | 1.00 |
| *Low* | 34 | 40 | **0.90** | 0.52 | 1.56 | 0.57 | **0.84** | 0.48 | 1.47 | 0.57 |
| *High* | 34 | 28 | **1.29** | 0.72 | 2.31 | | **1.23** | 0.68 | 2.22 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 83 | 84 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 83 | 77 | **1.09** | 0.71 | 1.68 | 0.69 | **1.03** | 0.66 | 1.60 | 0.90 |
| *Low* | 35 | 37 | **0.96** | 0.55 | 1.66 | 0.70 | **0.88** | 0.50 | 1.54 | 0.67 |
| *High* | 48 | 40 | **1.21** | 0.72 | 2.04 | | **1.17** | 0.69 | 1.98 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 82 | 81 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 67 | 72 | **0.92** | 0.58 | 1.45 | 0.72 | **0.85** | 0.53 | 1.35 | 0.48 |
| *Low* | 28 | 40 | **0.69** | 0.39 | 1.23 | 0.25 | **0.63** | 0.35 | 1.13 | 0.20 |
| *High* | 39 | 32 | **1.20** | 0.69 | 2.11 | | **1.12** | 0.64 | 1.99 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 79 | 81 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 59 | 62 | **0.98** | 0.61 | 1.56 | 0.92 | **0.91** | 0.56 | 1.48 | 0.71 |
| *Low* | 29 | 36 | **0.83** | 0.46 | 1.47 | 0.61 | **0.78** | 0.43 | 1.41 | 0.61 |
| *High* | 30 | 26 | **1.18** | 0.64 | 2.18 | | **1.10** | 0.59 | 2.04 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 1 pounds; High exposure: ≥ 1 pounds

***Table 3d. Relative risk estimates for prostate cancer with exposure to Organochlorine in California's Central Valley 2005 - 2006***

***Organochlorine***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 141 | 135 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 22 | 11 | **1.91** | 0.89 | 4.10 | 0.09 | **1.80** | 0.83 | 3.89 | 0.14 |
| *Low (†)* | 8 | 3 | **2.55** | 0.66 | 9.83 | 0.22 | **2.31** | 0.59 | 9.10 | 0.31 |
| *High (†)* | 14 | 8 | **1.68** | 0.68 | 4.12 | | **1.61** | 0.65 | 3.99 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 55 | 78 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 95 | 77 | **1.75** | 1.11 | 2.77 | 0.02 | **1.69** | 1.06 | 2.68 | 0.03 |
| *Low* | 58 | 62 | **1.33** | 0.81 | 2.18 | 0.00 | **1.28** | 0.77 | 2.12 | 0.00 |
| *High* | 37 | 15 | **3.50** | 1.75 | 6.99 | | **3.35** | 1.66 | 6.75 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 52 | 58 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 114 | 103 | **1.23** | 0.78 | 1.95 | 0.37 | **1.28** | 0.80 | 2.05 | 0.30 |
| *Low* | 55 | 55 | **1.12** | 0.66 | 1.89 | 0.50 | **1.16** | 0.67 | 1.99 | 0.44 |
| *High* | 59 | 48 | **1.37** | 0.80 | 2.34 | | **1.43** | 0.83 | 2.46 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 38 | 54 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 111 | 99 | **1.59** | 0.97 | 2.62 | 0.07 | **1.63** | 0.99 | 2.70 | 0.06 |
| *Low* | 49 | 51 | **1.37** | 0.77 | 2.42 | 0.10 | **1.39** | 0.78 | 2.49 | 0.09 |
| *High* | 62 | 48 | **1.84** | 1.05 | 3.22 | | **1.89** | 1.07 | 3.35 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 33 | 50 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 105 | 93 | **1.71** | 1.02 | 2.88 | 0.04 | **1.71** | 1.01 | 2.91 | 0.05 |
| *Low* | 46 | 48 | **1.45** | 0.80 | 2.64 | 0.07 | **1.47** | 0.80 | 2.69 | 0.08 |
| *High* | 59 | 45 | **1.99** | 1.11 | 3.57 | | **1.98** | 1.08 | 3.62 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 2.5 pounds; High exposure: ≥ 2.5 pounds

***Table 3e. Relative risk estimates for prostate cancer with exposure to Paraquat Dichloride in California's Central Valley 2005 - 2006***

***Paraquat Dichloride***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 118 | 125 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 45 | 21 | **2.27** | 1.28 | 4.04 | 0.01 | **2.09** | 1.17 | 3.76 | 0.01 |
| *Low (†)* | 8 | 2 | **4.24** | 0.88 | 20.36 | 0.02 | **4.08** | 0.84 | 19.83 | 0.04 |
| *High (†)* | 37 | 19 | **2.06** | 1.12 | 3.79 | | **1.88** | 1.01 | 3.50 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 47 | 62 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 103 | 93 | **1.46** | 0.91 | 2.34 | 0.12 | **1.43** | 0.89 | 2.31 | 0.14 |
| *Low* | 49 | 49 | **1.32** | 0.76 | 2.28 | 0.22 | **1.32** | 0.76 | 2.31 | 0.29 |
| *High* | 54 | 44 | **1.62** | 0.93 | 2.81 | | **1.55** | 0.89 | 2.71 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 49 | 54 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 117 | 107 | **1.20** | 0.76 | 1.92 | 0.43 | **1.23** | 0.76 | 1.98 | 0.39 |
| *Low* | 58 | 63 | **1.01** | 0.60 | 1.72 | 0.28 | **1.08** | 0.63 | 1.84 | 0.40 |
| *High* | 59 | 44 | **1.48** | 0.85 | 2.56 | | **1.44** | 0.82 | 2.52 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 41 | 52 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 108 | 101 | **1.36** | 0.83 | 2.22 | 0.22 | **1.35** | 0.82 | 2.23 | 0.23 |
| *Low* | 53 | 62 | **1.08** | 0.63 | 1.88 | 0.10 | **1.12** | 0.64 | 1.95 | 0.15 |
| *High* | 55 | 39 | **1.79** | 1.00 | 3.19 | | **1.73** | 0.96 | 3.12 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 33 | 48 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 105 | 95 | **1.61** | 0.95 | 2.71 | 0.08 | **1.59** | 0.93 | 2.71 | 0.09 |
| *Low* | 55 | 55 | **1.45** | 0.81 | 2.60 | 0.15 | **1.50** | 0.83 | 2.70 | 0.21 |
| *High* | 50 | 40 | **1.82** | 0.99 | 3.34 | | **1.71** | 0.92 | 3.20 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 0.4 pounds; High exposure: ≥ 0.4 pounds

***Table 3f. Relative risk estimates for prostate cancer with exposure to Benzimidazole Benomyl in California's Central Valley 2005 - 2006***

***Benzimidazole Benomyl***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 152 | 134 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 11 | 12 | **0.81** | 0.35 | 1.89 | 0.62 | **0.79** | 0.33 | 1.87 | 0.59 |
| *Low (†)* | 3 | 5 | **0.53** | 0.12 | 2.26 | 0.69 | **0.50** | 0.11 | 2.20 | 0.66 |
| *High (†)* | 8 | 7 | **1.01** | 0.36 | 2.85 | | **1.00** | 0.35 | 2.87 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 75 | 99 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 75 | 56 | **1.77** | 1.12 | 2.80 | 0.01 | **1.71** | 1.08 | 2.72 | 0.02 |
| *Low* | 36 | 28 | **1.70** | 0.95 | 3.02 | 0.05 | **1.68** | 0.94 | 3.02 | 0.08 |
| *High* | 39 | 28 | **1.84** | 1.04 | 3.25 | | **1.74** | 0.97 | 3.10 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 87 | 97 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 79 | 64 | **1.38** | 0.89 | 2.13 | 0.15 | **1.33** | 0.85 | 2.07 | 0.21 |
| *Low* | 37 | 35 | **1.18** | 0.68 | 2.03 | 0.24 | **1.18** | 0.68 | 2.06 | 0.37 |
| *High* | 42 | 29 | **1.61** | 0.93 | 2.81 | | **1.50** | 0.85 | 2.64 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 81 | 97 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 68 | 56 | **1.45** | 0.92 | 2.30 | 0.11 | **1.35** | 0.84 | 2.15 | 0.21 |
| *Low* | 27 | 29 | **1.11** | 0.61 | 2.03 | 0.12 | **1.05** | 0.57 | 1.94 | 0.22 |
| *High* | 41 | 27 | **1.82** | 1.03 | 3.21 | | **1.66** | 0.93 | 2.97 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 72 | 95 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 66 | 48 | **1.81** | 1.12 | 2.94 | 0.02 | **1.64** | 1.00 | 2.68 | 0.05 |
| *Low* | 27 | 23 | **1.55** | 0.82 | 2.92 | 0.04 | **1.47** | 0.77 | 2.79 | 0.13 |
| *High* | 39 | 25 | **2.06** | 1.14 | 3.71 | | **1.80** | 0.98 | 3.29 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 0.2 pounds; High exposure: ≥ 0.2 pounds

***Table 3g. Relative risk estimates for prostate cancer with exposure to Maneb in California's Central Valley 2005 - 2006***

***Maneb***

| Exposure Type | Frequency | | Crude | | | | Adjusted | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Control | OR | L95 | U95 | *p-value* | OR (*) | L95 | U95 | *p-value* |
| ***DX Year Exposure*** | | | | | | | | | | |
| *Missing* | 10 | 16 | - | - | - | | - | - | - | |
| *Unexposed* | 157 | 145 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 6 | 1 | **5.54** | 0.66 | 46.54 | 0.12 | **6.03** | 0.71 | 51.28 | 0.10 |
| *Low (†)* | 0 | 0 | **-** | - | - | - | **-** | - | - | - |
| *High (†)* | 6 | 1 | **5.54** | 0.66 | 46.54 | | **6.03** | 0.71 | 51.28 | |
| ***1974 - 1999*** | | | | | | | | | | |
| *Missing* | 23 | 7 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 118 | 121 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 32 | 34 | **0.97** | 0.56 | 1.66 | 0.90 | **0.94** | 0.54 | 1.63 | 0.83 |
| *Low* | 14 | 17 | **0.84** | 0.40 | 1.79 | 0.87 | **0.80** | 0.37 | 1.72 | 0.82 |
| *High* | 18 | 17 | **1.09** | 0.53 | 2.21 | | **1.08** | 0.53 | 2.22 | |
| ***Life time*** | | | | | | | | | | |
| *Missing* | 7 | 1 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 130 | 120 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 36 | 41 | **0.81** | 0.49 | 1.35 | 0.42 | **0.80** | 0.47 | 1.34 | 0.39 |
| *Low* | 20 | 24 | **0.77** | 0.40 | 1.46 | 0.70 | **0.75** | 0.39 | 1.45 | 0.67 |
| *High* | 16 | 17 | **0.87** | 0.42 | 1.80 | | **0.86** | 0.41 | 1.80 | |
| ***10 year prior DX*** | | | | | | | | | | |
| *Missing* | 24 | 9 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 119 | 114 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 30 | 39 | **0.74** | 0.43 | 1.27 | 0.27 | **0.71** | 0.41 | 1.24 | 0.23 |
| *Low* | 15 | 21 | **0.68** | 0.34 | 1.39 | 0.52 | **0.67** | 0.33 | 1.39 | 0.47 |
| *High* | 15 | 18 | **0.80** | 0.38 | 1.66 | | **0.76** | 0.36 | 1.61 | |
| ***15 year prior DX*** | | | | | | | | | | |
| *Missing* | 35 | 19 | **-** | - | - | | **-** | - | - | |
| *Unexposed* | 108 | 107 | **1.00** | - | - | | **1.00** | - | - | |
| *Exposed* | 30 | 36 | **0.83** | 0.47 | 1.44 | 0.50 | **0.79** | 0.45 | 1.39 | 0.42 |
| *Low* | 14 | 20 | **0.69** | 0.33 | 1.44 | 0.62 | **0.68** | 0.32 | 1.45 | 0.61 |
| *High* | 16 | 16 | **0.99** | 0.47 | 2.08 | | **0.92** | 0.43 | 1.97 | |

*: Adjusted for age, ethnicity and home pesticide use

†: Low exposure: > 0 and < 0.3 pounds; High exposure: ≥ 0.3 pounds

These results clearly show:

- Different estimates of relative risk are obtained when considering only diagnosis year exposures compared to exposures over time which includes life time, 1974 – 1999 and so on. However, these do not always result in a bias towards the null: the effect is pesticide-specific, which presumably is a result of the variation in application of pesticides over time. Pesticides that were more commonly applied recently will be affected differently from those more commonly applied decades ago.
- There appear to be significant increased risks of prostate cancer associated with exposure to methyl bromide, captan, simazine, organochlorine group, paraquat dichloride and benzimidazole benomyl, after adjusting for some common potential confounding factors including age, race and home pesticide usage. There doesn't seem to be increased risk for maneb use (with most ORs less than 1). Methyl bromide exposure during 1974-1999 increases the risk with OR 1.63 (1.03, 2.58); high level exposure to captan during 1974-1999 increases the risk with OR 1.91 (1.05, 3.50); those who were exposed to organochlorines during 1974-1999 have an increased risk with OR 1.69(1.06, 2.68).The magnitudes of the increased risks represented by adjusted odds ratios vary according to different exposures and exposure evaluation methods, ranging from 1 to 6, with large number calculated by using diagnosis year exposure, which can be seen as a proof of instability for using diagnosis year only.
- Methyl bromide, captan and organochlorine exposure all demonstrated multiple significantly increased ORs while simazine only showed significant risk for diagnosis year exposure; interestingly in most cases exposure to maneb resulted in decreased risks. We also noticed that all but the exposure to methyl bromide expressed an increasing trend in risk when comparing high level exposure to low level exposure. In fact, most low level exposure almost showed no increased risk while many high level exposures did. These results are in agreement with studies of occupational exposure to pesticides where exposure levels far exceed those to be expected in the residential environment, which we have measured here. These results must be heeded with caution because of they are subject to missing values and limited sample size.

## Recruitment of an unbiased sample of control subjects by visiting residential tax assessor parcel units in the study area.

We conducted home visits of randomly-selected tax assessor parcel residential units, to recruit control subjects. We made 8 field trips into the Central Valley, each consisting of 3 days work by 2 teams of 2 interviewers. Key characteristics of this effort are:

- We visited 434 households from 1,093 eligible parcels. We also attempted to visit two additional neighbors for each parcel. To date we have visited 813 such neighbors neighbors.
- We recruited 23 control subjects, who have been interviewed.
- We have developed software for a handheld computer (PDA) with a built in GPS device that also validates the location of residential parcels (for future validation of residential history in our GIS) – this PDA is also used as the primary data collection tool for enumerating households and collecting baseline eligibility data for controls.

## Selection bias in cases and controls.

In this study, we can estimate sample selection bias for pesticide exposures, because the GRAPES program requires only a latitude/longitude in order to provide pesticide exposure estimates. While we know little about the cases who did not respond, and we know nothing about the eligible controls who did not respond, we do know their locations at recruitment (diagnosis address for Registry cases, and tax assessor parcel for all selected control locations).

We generated pesticide exposures for all cases (n=670) we selected from the Cancer Registry, based on their diagnosis address. We likewise generated pesticide exposures for all tax assessor parcels that we drew control subjects from (n=3,689). We then generated average annual exposures for the 1974-1999 time period for these locations (which assumes that no one moved during that time period) and compared those to the exposures obtained for diagnosis address (for cases, or interview address for controls).

Table 4 provides the average annual exposures for selected cases and controls (referred to as the "pool" cases/controls) and for those included in the analysis ("sample").

We calculated crude ORs for the observed exposures (note: these do not match the ORs from previous tables, because they are based on diagnosis address only), and then adjusted ORs based on the exposures experienced by the "pool" cases and controls. The latter could be considered population-based estimates, not affected by sample selection bias.

Key findings:

- There was clear evidence of under-estimation of pesticide exposures in control subjects, as we would expect in most epidemiological studies
- However, there was also under-estimation of exposures for cases.

- "True" ORs were affected by sample selection bias: for example, for Methyl Bromide, the OR in the case-control sample was 1.50, whereas the OR in the underlying population was only 1.35. This arose due to differential misclassification of exposure (cases experienced some under-estimation of exposure, but controls experienced more). Therefore, in this analysis we over-estimated the true OR for MB exposure.
- The magnitude, and more importantly, the DIRECTION of misclassification varied by pesticide. For example, in contrast to MB, for captan there was greater under-estimation cases than controls, resulting in an under-estimation of the true OR (observed = 1.56, "true" = 1.80).
- In the worst case, the effect of organochlorine exposure appeared to have been over-estimated as OR = 2.27, whereas the "true" OR was only 1.37.
- It should be noted that none of these analyses, specifically the "true" ORs, are adjusted for any of the other factors considered in previous analyses (E.g. age). This is because we do not have those data for the 'pool' of controls (we do have age, race and tumor characteristics for cases, but without that information in the non-responding controls, it cannot be used in analysis).

***Table 4***. Average annual exposure summary during 1974 - 1999 based on samples for various pesticides.

| *Chemical /Sample* | *Average* | *Total* | *Exposed* | *Exposed%* | *Odds Ratio** |
|---|---|---|---|---|---|
| ***Methyl Bromide*** | | | | | |
| Control Pool | 21.43 | 3689 | 1962 | 53.2% | |
| Control Sample | 16.23 | 150 | 66 | 44.0% | |
| Case Pool | 36.34 | 670 | 406 | 60.6% | 1.35 (1.14, 1.60) |
| Case Sample | 34.28 | 170 | 92 | 54.1% | 1.50 (0.97, 2.33) |
| ***Captan*** | | | | | |
| Control Pool | 1.34 | 3689 | 1253 | 34.0% | |
| Control Sample | 1.17 | 150 | 45 | 30.0% | |
| Case Pool | 2.98 | 670 | 322 | 48.1% | 1.80 (1.52, 2.12) |
| Case Sample | 2.15 | 170 | 68 | 40.0% | 1.56 (0.98, 2.48) |
| ***Simazine*** | | | | | |
| Control Pool | 1.84 | 3689 | 1655 | 44.9% | |
| Control Sample | 1.26 | 150 | 58 | 38.7% | |
| Case Pool | 3.29 | 670 | 348 | 51.9% | 1.33 (1.13, 1.57) |
| Case Sample | 3.50 | 170 | 82 | 48.2% | 1.48 (0.95, 2.31) |
| ***Oganochlorine*** | | | | | |
| Control Pool | 2.73 | 3689 | 2265 | 61.4% | |
| Control Sample | 1.27 | 150 | 74 | 49.3% | |
| Case Pool | 4.36 | 670 | 459 | 68.5% | 1.37 (1.15, 1.63) |
| Case Sample | 4.45 | 170 | 117 | 68.8% | 2.27 (1.44, 3.58) |
| ***Paraquat Dichloride*** | | | | | |
| Control Pool | 1.18 | 3689 | 2544 | 69.0% | |
| Control Sample | 1.54 | 150 | 81 | 54.0% | |
| Case Pool | 1.99 | 670 | 506 | 75.5% | 1.39 (1.15, 1.68) |
| Case Sample | 2.30 | 170 | 124 | 72.9% | 2.30 (1.44, 3.66) |
| ***Benzimidazole Benomyl*** | | | | | |
| Control Pool | 0.42 | 3689 | 1651 | 44.8% | |
| Control Sample | 0.62 | 150 | 57 | 38.0% | |
| Case Pool | 0.75 | 670 | 359 | 53.6% | 1.43 (1.21, 1.68) |
| Case Sample | 0.67 | 170 | 80 | 47.1% | 1.45 (0.93, 2.27) |
| ***Maneb*** | | | | | |
| Control Pool | 0.43 | 3689 | 848 | 23.0% | |
| Control Sample | 0.37 | 150 | 28 | 18.7% | |
| Case Pool | 0.62 | 670 | 203 | 30.3% | 1.46 (1.22, 1.75) |
| Case Sample | 0.45 | 170 | 44 | 25.9% | 1.52 (0.89, 2.60) |

* Odds ratios and their confidence intervals based on corresponding samples

## Evidence of diagnostic bias in cases.

One reason that we might observe an effect between pesticide exposure and prostate cancer is if the availability of screening differed between pesticide exposed and unexposed areas. That is, if screening is more readily accessible in urban areas (with low pesticide exposures) it may be that there are more cases discovered in areas with lower pesticide exposures than in areas with higher pesticide exposures. This is a diagnostic bias for cases.

In order to test that possibility, we stratified analyses by stage of diagnosis. If there was evidence of diagnostic bias, we might expect more unexposed localized cases of disease, and therefore a lower OR in the localized cases than in regional and higher stage disease. Table 6 provides stratified analyses by stage ("Regional" refers to all stages other than localized disease). Only for Benomyl did there appear to be evidence of higher relative risk in regional (and higher) stages than for localized disease. We conclude that there is no particular reason to believe that diagnostic bias affects the results we have observed.

***Table 6***. Analysis for prostate cancer stages based on average annual exposure during 1974-1999

| | Frequency | | | Adjusted Odds Ratio Estimates | | | |
|---|---|---|---|---|---|---|---|
| *Chemical/Stage* | *Missing* | *Unexposed* | *Exposed* | *OR** | *L95* | *U95* | *p-value* |
| ***Methyl Bromide*** | | | | | | | |
| ***Controls*** | 7 | 85 | 70 | 1 | - | - | - |
| ***Localized*** | 18 | 52 | 75 | 1.79 | 1.08 | 2.99 | 0.02 |
| ***Regional*** | 5 | 11 | 12 | 1.33 | 0.53 | 3.30 | 0.54 |
| ***Captan*** | | | | | | | |
| ***Controls*** | 7 | 104 | 51 | 1 | - | - | - |
| ***Localized*** | 18 | 79 | 48 | 1.11 | 0.65 | 1.91 | 0.70 |
| ***Regional*** | 5 | 13 | 10 | 1.42 | 0.55 | 3.66 | 0.47 |
| ***Simazine*** | | | | | | | |
| ***Controls*** | 7 | 87 | 68 | 1 | - | - | - |
| ***Localized*** | 18 | 68 | 59 | 1.01 | 0.61 | 1.69 | 0.96 |
| ***Regional*** | 5 | 14 | 9 | 0.82 | 0.32 | 2.08 | 0.68 |
| ***Organochlorine*** | | | | | | | |
| ***Controls*** | 7 | 78 | 77 | 1 | - | - | - |
| ***Localized*** | 18 | 45 | 82 | 1.66 | 0.99 | 2.78 | 0.06 |
| ***Regional*** | 5 | 10 | 13 | 1.29 | 0.51 | 3.26 | 0.58 |
| ***Paraquat Dichloride*** | | | | | | | |
| ***Controls*** | 7 | 62 | 93 | 1 | - | - | - |
| ***Localized*** | 18 | 39 | 88 | 1.41 | 0.82 | 2.40 | 0.21 |
| ***Regional*** | 5 | 8 | 15 | 1.24 | 0.48 | 3.23 | 0.66 |
| ***Benzimidazole Benomyl*** | | | | | | | |
| ***Controls*** | 7 | 99 | 56 | 1 | - | - | - |
| ***Localized*** | 18 | 65 | 62 | 1.75 | 1.04 | 2.95 | 0.03 |
| ***Regional*** | 5 | 10 | 13 | 2.56 | 1.01 | 6.50 | 0.05 |
| ***Maneb*** | | | | | | | |
| ***Controls*** | 7 | 121 | 34 | 1 | - | - | - |
| ***Localized*** | 18 | 99 | 28 | 0.89 | 0.48 | 1.65 | 0.70 |
| ***Regional*** | 5 | 19 | 4 | 0.75 | 0.23 | 2.49 | 0.64 |

*: Adjusted for age, ethnicity and home pesticide use

## C. KEY RESEARCH ACCOMPLISHMENTS:

Results clearly show:

- Different estimates of relative risk are obtained when considering only diagnosis year exposures compared to lifetime exposures. However, these do not always result in a bias towards the null: the effect is pesticide-specific, which presumably is a result of the variation in application of pesticides over time. Pesticides that were more commonly applied recently will be affected differently from those more commonly applied decades ago.
- There appear to be significant increased risks of prostate cancer associated with exposure to methyl bromide, captan, simazine and organochlorine group after adjusting to some common potential confounding factor including age, race and home pesticide usage (this is currently a yes/no variable, we are presently investigating the actual pesticides used in the home). The magnitudes of the risks represented by adjusted odds ratios vary according to different exposures and exposure evaluation methods, ranging from 1 to 4, with methyl bromide, captan and organochlorine all showing multiple significant ORs while simazine only showing significant risk for high diagnosis year exposure. We also noticed that all but the exposure to methyl bromide expressed an increasing trend in risk when comparing high level exposure to low level exposure. In fact, most low level exposure almost showed no increased risk while many high level exposures did.
- While these results are based on relatively small numbers, and some do not reach statistical significance at the 5% level, most are verified in the analyses of the underlying case series and random selection of parcel controls used in the bias analysis. For some pesticides in that analysis, while the ORs were baised slightly towards the null, the 'true' OR remained raised, and statistically significantly elevated.

With respect to Aim 2, it appears that our method of conducting a case-control study of prostate cancer risk factors in California's Central Valley will likely result in:

- An unbiased sample of cases with respect to tumor and individual characteristics. However, for pesticide exposures, bias in exposure estimation will vary by pesticide.
- Sufficient DNA for multiple SNPs
- A more accurate method for assessing ambient pesticide exposure than has been previously utilized.
- The method of collecting control subjects using home visits needs to be made more efficient – the amount of effort required to obtain each eligible control subject greatly exceeded our expectations. One way we addressed this issue was to also sample the neighbors of selected control dwellings, and in our upcoming analyses we will determine the representativeness of all of our control approaches (by comparing pesticide exposures in respondent versus selected control dwellings).
- There is a clear impact of selection bias on the study of pesticide exposure and cancer outcome. This has not previously been able to be assessed in any study we are aware of, and has undoubtedly been relevant to all previous studies.

- Despite that bias, which can be differential or non-differential depending on pesticide, there remain statistically significant effects of pesticide exposures on prostate cancer (even with this small sample size).
- There is no particular evidence of diagnostic bias in the cases.

When expanding this study to a full scale case-control study, we should:

- Obtain and process data from 2000 onwards from PUR and LUI (currently available)
- Design a follow-up process to immediately quantify DNA yield in specimens and return to the participant and ask for another specimen if the yield is below 10,000 ng

## D. REPORTABLE OUTCOMES:

- The questionnaire used in this study was adapted from those used elsewhere, but will be made available online at the time of publication of our report of this project (particularly the questionnaire on residential history, which is central to the exposure analysis algorithm).
- The GRAPES software was developed during this study, and is available from the PI (Cockburn@usc.edu). Currently it is on a shared volume on our server, and is not made openly available because the documentation regarding its use is not complete. To date, the software has been used under supervision of the PI for 3 additional studies of pesticide exposure in the Central Valley.
- Manuscripts outlining the automation of the GRAPES process are in process. Current manuscripts using the methods developed with funds from this grant:

    - Jennifer Marusek, **Myles Cockburn**, Paul Mills, Beate Ritz. *Controls selection and pesticide exposure assessment via GIS in population based prostate cancer studies* Am J Prev Med 2006; 30:109–116
    - Goldberg D.W., Zhang X., Marusek J.C., Wilson J.P., Ritz B., **Cockburn M.G**. *Development of an Automated Pesticide Exposure Analyst for California's Central Valley*. Proceedings of the Urban and Regional Information Systems Association GIS in Public Health Conference, New Orleans, LA, 2007. pp 136-156.
    - Daniel Goldberg, John Wilson, Craig Knoblock, Beate Ritz, **Myles G Cockburn** *An effective and efficient approach for manually improving geocodes* Int Jnl Health Geographics, 2008, 7:60-79
    - Costello, S.., **Cockburn M.G,** Zhang X., Ritz B., *"Parkinson Disease and Residential Exposure to Maneb and Paraquat from Agricultural Applications in the Central Valley of California"* American Jnl of Epidemiology (in press)

- Other manuscripts currently being written include the following topics:
    - Comparison of diagnosis address exposure and exposures using lifetime residential history in case-control data. Assess bias in considering only

DX exposure, and build model of appropriate time sequence of exposure (i.e. time between exposure and DX, as opposed to age-specific exposure or total cumulative exposure). Aim is to come up with an exposure matrix that is biologically meaningful for specific pathways hypothesized. Compare mean exposures and resulting relative risks: DX-only exposure versus lifetime with known residential history: Versus age-specific exposure: Versus cumulative exposure (Age-weighted)

- What is the effect of missing residential history data on residential history of pesticide exposure? Use case-control data to test the effect of various missing data imputation models to fill in holes:

  - Impact on lifetime versus age-specific, versus prior-to-DX specific exposures

  - Also analyze impact of missing pesticide exposure data (1970-99 versus other times)

  - Consider specific impacts of missing data from migrant populations (we know where the people missing pesticide exposure lived)

## E. CONCLUSION:

This study provides evidence that pesticide exposures appear to be strong risk factors for prostate cancer.

The study is slightly limited by sample size, but its purpose was to provide pilot data to justify a full scale case-control study of pesticide exposure in the development of prostate cancer. We believe that our preliminary results argue strongly for the need for a large-scale case-control study of the impact of pesticide exposures on prostate cancer.

If indeed pesticide exposure is associated with prostate cancer, the following should be considered:

- Ambient exposure to pesticides (i.e. exposure at residence, not occupational exposure) might explain increased risk of prostate cancer in certain geographical groups
- The impact of exogenous hormone exposure on prostate cancer might be substantial
- More research is required to determine what mechanisms cause pesticides to increase of prostate cancers – while these are presumably related to the hormone-mimicking affects of some pesticides, the exact mechanism, and therefore a means of prevention of prostate cancer, remain unknown.

**F. Bibliography of all publications and meeting abstracts**

Manuscripts


- Jennifer Marusek, **Myles Cockburn**, Paul Mills, Beate Ritz. *Controls selection and pesticide exposure assessment via GIS in population based prostate cancer studies* Am J Prev Med 2006; 30:109–116
- Goldberg D.W., Zhang X., Marusek J.C., Wilson J.P., Ritz B., **Cockburn M.G**. *Development of an Automated Pesticide Exposure Analyst for California's Central Valley*. Proceedings of the Urban and Regional Information Systems Association GIS in Public Health Conference, New Orleans, LA, 2007. pp 136-156.
- Daniel Goldberg, John Wilson, Craig Knoblock, Beate Ritz, **Myles G Cockburn** *An effective and efficient approach for manually improving geocodes* Int Jnl Health Geographics, 2008, 7:60-79
- Costello, S.., **Cockburn M.G,** Zhang X., Ritz B., *"Parkinson Disease and Residential Exposure to Maneb and Paraquat from Agricultural Applications in the Central Valley of California"* American Jnl of Epidemiology (in press)


Abstracts:


- *Getting the most out of automated GIS for longitudinal exposure assessment in environmental epidemiology* Daniel W. Goldberg, John P. Wilson and Myles G. Cockburn (ISEE, Mexico City, 2007)
- *Prostate cancer risk associated with ambient pesticide exposure in California's Central Valley* Myles Cockburn, Paul Mills (PHI), Xinbo Zhang, John Zadnick, Jennifer Marusek, Beate Ritz (UCLA) (PCRPCures, Atlanta, 2007)
- Development of a Pesticide Exposure Analyst for the California's Central Valley Daniel W. Goldberg, Myles Cockburn, Xinbo Zhang and Beate Ritz (URISA Health, New Orleans, 2007)


**G. List of personnel receiving pay from the research effort.**

Myles Cockburn, PhD (PI)
Jennifer Marusek, MSc (Project Coordinator, 2006-2007)
Marlene Caldera (Project Coordinator, 2007-8)
Daniel Goldberg, MS (PhD Student)
Xinbo Zhang, MS (PhD Student)
David Penson, MD (Clinical advisor)
Paul Mills, PhD (subcontract PI)
Beate Ritz, PhD, MD (subcontract PI)
Sadie Costello (PhD Student, UCLA, under Dr Ritz)
Vygandys Relys (Project Coordinator, UCLA, under Dr Ritz)

**REFERENCES:**

1. **Ross, R.K. and D. Schottenfeld, *Prostate cancer*. Cancer Epidemiology and Prevention, 2nd Edition, ed. D. Schottenfeld and J.F. Fraumeni. 1996, New York: Oxford University Press. 1180-1206.**
2. **Ferlay, J., et al., *Cancer Incidence in Five Continents*. Vol. VII. 1997, Lyon: IARC.**
3. **Hsing, A.W., *Hormones and prostate cancer: what's next?* Epidemiologic Reviews., 2001. 23(1): p. 42-58.**
4. **Keller-Byrne, J.E., S.A. Khuder, and E.A. Schaub, *Meta-analyses of prostate cancer and farming.* American Journal of Industrial Medicine., 1997. 31(5): p. 580-6.**
5. **Janssens, J.P., et al., *Pesticides and mortality from hormone-dependent cancers.* European Journal of Cancer Prevention., 2001. 10(5): p. 459-67.**
6. **Parent, M.E. and J. Siemiatycki, *Occupation and prostate cancer.* Epidemiologic Reviews., 2001. 23(1): p. 138-43.**
7. **Tessier, D.M. and F. Matsumura, *Increased ErbB-2 tyrosine kinase activity, MAPK phosphorylation, and cell proliferation in the prostate cancer cell line LNCaP following treatment by select pesticides.* Toxicological Sciences., 2001. 60(1): p. 38-43.**
8. **Alavanja, M.C., et al., *Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort.* American Journal of Epidemiology., 2003. 157(9): p. 800-14.**
9. **Mills, P.K., *Correlation analysis of pesticide use data and cancer incidence rates in California counties.* Archives of Environmental Health, 1998. 53(6): p. 410-3.**
10. **Dich, J. and K. Wiklund, *Prostate cancer in pesticide applicators in Swedish agriculture.* Prostate., 1998. 34(2): p. 100-12.**
11. **Ames, R.G., et al., *Protecting agricultural applicators from over-exposure to cholinesterase-inhibiting pesticides: perspectives from the California programme.* Journal of the Society of Occupational Medicine., 1989. 39(3): p. 85-92.**
12. **Brouwer, D.H., E.J. Brouwer, and J.J. van Hemmen, *Estimation of long-term exposure to pesticides.* American Journal of Industrial Medicine., 1994. 25(4): p. 573-88.**
13. **Savitz, D.A., et al., *Male pesticide exposure and pregnancy outcome.* American Journal of Epidemiology., 1997. 146(12): p. 1025-36.**
14. **Garcia, A.M., *Occupational exposure to pesticides and congenital malformations: a review of mechanisms, methods, and results.* American Journal of Industrial Medicine., 1998. 33(3): p. 232-40.**